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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ATUL VARADHACHARY and KAREL PETRAK

Appeal 2009-3669
Application 10/728,521
Technology Center 1600

Decided:[1] May 12, 2009

Before DONALD E. ADAMS, ERIC GRIMES and STEPHEN WALSH, *Administrative Patent Judges*.

WALSH, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method of treating bacteremia with oral administration of an N-terminal lactoferrin variant. The Patent Examiner rejected the claims as obvious and provisionally rejected the claims for obviousness-type double patenting. We have jurisdiction under 35 U.S.C. § 6(b). We affirm the obviousness

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, begins to run from the decided date shown on this page of the decision. The time period does not run from the Mail Date (paper delivery) or Notification Date (electronic delivery).

rejection and vacate the provisional obviousness-type double patenting rejection.

STATEMENT OF THE CASE

The Specification states that the invention relates to methods of treating bacteremia, sepsis, septic shock or related conditions. (Spec. 1:[0002].) The treatment could involve oral administration of lactoferrin alone or in combination with standard therapies. (*Id.*) The claims on appeal more particularly require a lactoferrin composition comprising a percentage of an N-terminal variant of lactoferrin.

Appellants state that the grounds of rejection on appeal are as follows:

- claims 1, 7, 14, 17-20, 26-32 and 38-40 under 35 U.S.C. § 103(a) as unpatentable over Van Bree;[2] and
- claims 1, 7-10, 14-20, 26-32 and 38-40 under the judicially created doctrine of obviousness-type double patenting (App. Br. 7, Reply Br. 3).

The Examiner states that the grounds of rejection set out in the Appeal Brief correctly sets out the grounds of rejection (Ans. 2).

The claims have not been argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). Claim 1 is representative and reads as follows:

1. A method of treating bacteremia comprising the step of

administering orally to a subject an effective amount of a lactoferrin composition comprising at least 1% to at least 50% w/w of an N-

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[2] Int'l Pub. No. WO 01/72322 A2, by Van Bree et al., published Oct. 4, 2001.

terminal lactoferrin variant to provide an improvement in the bacteremia of said subject,

wherein the improvement is selected from the group consisting of attenuating sepsis, attenuating septic shock, attenuating organ failure, decreasing morbidity and decreasing mortality,

wherein the N-terminal lactoferrin variant has a deletion, substitution, or combination thereof, of from 1 to 16 N-terminal amino acid residues and

wherein the N-terminal lactoferrin variant retains the same biological function as full length lactoferrin.

OBVIOUSNESS

The Issues

The Examiner's position is that Van Bree taught treating sepsis by orally administering N-terminal lactoferrin (LF) variants. (Ans. 3.) The Examiner found that "[a]lthough the reference does not provide a specific example for a method of treating bacteremia . . . it indicates a high dose of hLF and/or LF variant (e.g., N-terminal variant) having the biological activity of natural LF can be orally administered." (Ans. 4.) The Examiner found that Van Bree taught "a method of treating large scale (bacterial) infection, blood-borne infection (sepsis) as well as the inflammation resulting from an infection . . . by parenteral and/or oral administration of LF/variants." (*Id.*) The Examiner concluded it would have been obvious for one of ordinary skill in the art to follow Van Bree's teaching that oral administration could be used alone, "which results in the claimed invention." (*Id.*)

Appellants contend that "(1) *the prior art does not teach all of Applicant's claim limitations*, and (2) *no rationale to support an obviousness rejection is presented*." (App. Br. 7.) According to Appellants, (1) Van Bree did not teach oral administration without parenteral administration (*id.* at 8), (2) Van Bree did not teach N-terminal LF variants having full-length activity (*id.* at 10), and (3) Van Bree did not teach oral LF administration to treat sepsis (*id.*). Appellants argue that one of skill in the art would have had "no impetus to modify the prior art into something closer to the claimed invention as a whole because the knowledge in the art taught such changes (*e.g.* orally administered LF) would not work." (*Id.* at 12.)

Appellants also assert that there was "neither a reasonable expectation of success nor the necessary measure of predictability in the Examiner's advanced modification." (App. Br. 13.) Appellants point to Kuhara[3] as evidence that "[i]t was known . . . that lactoferrin is not systemically bioavailable when ingested, and that high oral doses of lactoferrin do not significantly raise plasma lactoferrin levels (Kuhara, page 197, lines 8-10)." (Reply Br. 5.) According to Appellants, "one of skill in the art would not assume that parenteral administration and oral administration were equivalent," and "Kuhara teaches away from using oral dosages of lactoferrin to treat the conditions and diseases that Van Bree discloses as needing high dosage parenteral administration, such as bacteremia and sepsis." (*Id.* at 5-6.)

The issues Appellants present are:

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[3] Tetsuya Kuhara et al., *Orally Administered Lactoferrin Exerts an Antimetastatic Effect and Enhances Production of IL-18 in the Intestinal Epithelium*, 38 NUTRITION AND CANCER 192 (2000).

Whether Van Bree taught oral administration alone to treat sepsis;

Whether Van Bree taught N-terminal LF variants having full-length activity;

Whether the Examiner presented a rationale to support the obviousness rejection; and

Whether there would have been a reasonable expectation of success for treating sepsis with oral LF variant administration?

An additional issue is whether Appellants' open claim language "comprising" the step of administering orally distinguishes Van Bree's method in which "[o]ral administration can also be used, optionally but not necessarily, in conjunction with parenteral administration."

Findings of Fact

1. Van Bree taught that lactoferrin (LF) variants were useful for disease treatment. (3:31.)
2. Van Bree taught that "LF variants have the biological activities of natural LF, *e.g.*, binding to high affinity receptors on cells, but with reduced binding, relative to natural LF, to heparin, DNA, [etc.]." (3:33-4:1.)
3. Van Bree taught that "an advantage to the use of the LF variants is that the desired physiological effect can be achieved while avoiding side effects caused by the binding of natural LF to heparin, DNA, [etc.]" (4:3 – 4:5.)
4. Van Bree taught exemplary human LF N-terminal variants. (4:13-14; 27:10-30.)

5. Van Bree taught "variants of LF have 1-4 arginine residues from the first basic cluster (*i.e.*, residues 2-5) deleted." (4:13-14; 5:6-28.)
6. Van Bree taught administering LF variants to treat "blood-borne infection (sepsis)" (20:24-27.)
7. According to Van Bree, "[o]ral administration can also be used, optionally but not necessarily, in conjunction with parenteral administration." (23:24-26.)
8. Van Bree taught that the concentration of the lactoferrin in the composition administered "can vary widely, *i.e.*, from less than about 0.1% by weight, usually being at least about 1% by weight to as much as 20% by weight or more." (24:10-12.)
9. Van Bree described solid and liquid oral dosage forms; oral administration of LF produced in milk from a transgenic animal had an advantage because little or no purification was necessary for human consumption. (26:16-21.)
10. Kuhara described lactoferrin [LF] as a protein present in milk, having a number of physiological functions including anti-microbial activity. (192:left col.)
11. Kuhara "examined the effects of orally administered bLF [bovine LF] on antimetastatic host defense through the intestinal immune system." (192:right col.)
12. Kuhara reported that "oral administration of bLF induced IL-18 production in the small intestine, which may modulate immunologic function, and inhibited formation of lung metastatic colonies." (192:right col.)

13. Kuhara reported that "[a]fter the final oral administration of bLF, serum bLF concentrations in samples from the portal vein and heart were below the limits of detection . . . . These results suggested that bLF and bLFH [pepsin hydrolysate of bLF] may affect the immune system in the gastrointestinal tract." (195:right col.)
14. According to Kuhara, "LF cannot be absorbed as the undigested form, because it is a large molecule, so it is unlikely that it had direct effects in the present study." (197:left col.)
15. We find that by concluding that oral LF was unlikely to have direct effects, Kuhara implied that orally administered LF likely had indirect effects.
16. Kuhara stated "it is of interest whether LF and IL-18 exert functions in collaboration for the mucosal immunity and whether IL-18 production in local mucosal tissue, for example, the intestinal epithelium, influences not only mucosal immunity but the immune system of the whole body." (198:left col.)

Principles of Law

Obviousness is a question of law based on fact findings. The scope and content of the prior art are determined; differences between the prior art and the claims at issue are ascertained; the level of skill in the art is resolved; and objective record evidence of nonobviousness is considered. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Against that background, the obviousness or nonobviousness of the subject matter is determined. *Id.; In re Kahn*, 441 F.3d 977, 985 (Fed. Cir. 2006).

"[A] prima facie case of obviousness arises when the ranges of a claimed composition overlap the ranges disclosed in the prior art". *In re Harris*, 409 F.3d 1339, 1341 (Fed. Cir. 2005). A prior art reference is said to teach away from an applicant's invention "when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). "When prior art contains apparently conflicting references, the Board must weigh each reference for its power to suggest solutions to an artisan of ordinary skill. The Board must consider all disclosures of the prior art." *In re Young*, 927 F.2d 588, 591 (Fed. Cir. 1991). "The prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed." *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). "Obviousness does not require absolute predictability of success. . . . [A]ll that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988).

"The transition 'comprising' in a method claim indicates that the claim is open-ended and allows for additional steps." *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368 (Fed. Cir. 2003).

Analysis

Claim 1 recites a method "comprising the step of administering orally." The transitional term "comprising" is a signal that the claim is open-ended and allows for additional steps. *Invitrogen*, 327 F.3d at 1368.

Appellants argue as if their claims exclude the parenteral LF administration disclosed in Van Bree, but the claims are not exclusionary. "In simple terms, a drafter uses the phrase 'consisting of' to mean 'I claim what follows and nothing else.' A drafter uses the term 'comprising' to mean 'I claim at least what follows and potentially more.'" *Vehicular Technologies Corp. v. Titan Wheel Int'l, Inc.*, 212 F.3d 1377, 1383 (Fed. Cir. 2000). Because claim 1 is to a method "comprising" an oral administration step, it claims at least an oral administration step. Appellants argue that Van Bree described oral and parenteral administration together. (App. Br. 8.) We conclude that claim 1, properly interpreted, does not define a difference from the combination of oral and parenteral administration that Van Bree described.

Appellants have two lines of argument against obviousness: "(1) *the prior art does not teach all of Applicant's claim limitations,* and (2) *no rationale to support an obviousness rejection is presented.*" (App. Br. 7.)

The first line of argument disputes the Examiner's fact finding regarding the scope and content of the prior art. The evidence supports the Examiner on each point. First, Van Bree expressly taught oral administration without parenteral administration: "[o]ral administration can also be used, optionally but not necessarily, in conjunction with parenteral administration." (FF8.) The oral treatment was for sepsis. (FF7.) Second, Van Bree expressly described N-terminal LF variants having full-length activity: "LF variants have the biological activities of natural LF." (FF2; FF3.) Van Bree's N-terminal variants were the kind recited in Appellants' claims. (FF5; FF6.) Even if, hypothetically, Van Bree had taught oral administration only in conjunction with parenteral administration as Appellants argue (App. Br. 9), the rejection would have to be affirmed

because Appellants' claims are open-ended and include methods comprising both oral and parenteral administration.

The second line of argument concerns the purported lack of a "rationale" to support the obviousness rejection. (App. Br. 7.) The Examiner found it would have been obvious to use Van Bree's method, which the Examiner found was effective to treat sepsis. (Ans. 4.) Appellants rely on case law dealing with the combination of teachings from more than one reference, where the court held that the reasons for combining elements from various references must be articulated. Here, there is no combination, and the rationale that it would have been obvious to employ Van Bree's effective method, despite the absence of a working example, was sufficient.[4]

Appellants argue that one of skill in the art, aware of Van Bree and Kuhara, would not have believed that oral administration could provide the "same benefits" of systemic LF provided parenterally in high dosages. (App. Br. 9.) Appellants also assert that there was "neither a reasonable expectation of success nor the necessary measure of predictability in the Examiner's advanced modification." (*Id.* at 13.) However, the Examiner did not advance a modification to Van Bree's method. Instead, the Examiner concluded it would have been obvious to orally administer a composition comprising an N-terminal lactoferrin variant, which Van Bree disclosed as one method of treating sepsis, and that doing so would have

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[4] The Examiner may have been unaware that "anticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabling to one of skill in the art." *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1379 (Fed. Cir. 2001).

been the invention Appellants now claim. (Ans. 4.) We find that one of ordinary skill in the art would have had a reasonable expectation of success in using Van Bree's method for several reasons.

First, the claims do not call for the "same benefits" of parenteral high dosages. Claim 1 simply requires an amount effective for "attenuating" such conditions as sepsis, septic shock or organ failure, or for decreasing morbidity or mortality. Claim 1 is not written in terms that compare the effect achieved to the benefits of parenteral administration, nor have Appellants pointed to a special definition for "attenuating."

Second, Kuhara evidenced that orally administered LF had antimetastatic effects in the lungs, i.e., outside the digestive system. (FF13.) Evidence that oral administration had a beneficial effect did not disparage or teach away from oral administration. *See Gurley*, 27 F.3d at 553. Even if parenteral administration would have been expected to have a better effect in attenuating sepsis than oral administration, that also would not have disparaged the expected ability of oral administration to attenuate sepsis. *See Fulton*, 391 F.3d at 1201. Based on the results achieved, Kuhara theorized that orally administered LF may have a systemic effect such as stimulating the immune system in the intestines, and influencing the whole body's immune system. (FF14; FF16.) We must consider all disclosures of the prior art, including all of Kuhara. *Young*, 927 F.2d at 591. Appellants provide no evidence that those of skill in the art would discount Kuhara's disclosures that (i) orally administered LF had effects beyond the digestive system, and (ii) orally administered LF may have caused those effects by generally stimulating the immune system. As the Examiner found, Kuhara was positive evidence that orally administered LF was known to have

beneficial effects even when it did not cause a systemic increase in LF levels. (Ans. 9-15.)

Attorney argument that a result would not have been expected does not take the place of evidence. "It is well settled that unexpected results must be established by factual evidence." *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984). Thus, we do not agree that knowledge in the art taught that orally administered LF would not work. *See* App. Br. 12. Further, Appellants have not accounted for the effect "comprising" has on the scope of their claims. The claims must be interpreted as open to the inclusion of other steps, such as Van Bree's parenteral administration coupled with oral administration, which undermines the significance of Appellants' unexpected results argument.

Finally, although Van Bree's lactoferrin composition may comprise from 0.1 % to 20 % of an N-terminal lactoferrin variant, Appellants have not argued that their claimed range of at least 1% to at least 50% is a nonobvious distinction. *See, e.g, Harris*, 409 F.3d at 1341.

PROVISIONAL OBVIOUSNESS-TYPE DOUBLE PATENTING

The Issue

The Examiner's position is that the current claims are an obvious variation of copending claims 16-22, 26-30 and 50-51 in Application No. 10/663,258, which are said to claim a method of enhancing the local or systemic immune system by oral lactoferrin administration. (Ans. 5.)

Appellants contend that they are not required to address the provisional rejection until such time as the copending claims actually issue and the rejection becomes non-provisional. (App. Br. 14.) While

Appellants do not concede the merits of the rejection, they suggest it is proper for the Board to withhold opinion on the rejection.

Principle of Law

If an invention claimed in a later patent is not identical to the invention claimed in an earlier patent, but is instead an "obvious" variation of the invention recited in the claims of the earlier patent, then the second patent is invalid under the judicially-created doctrine called "nonstatutory," or "obviousness-type double patenting." *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955 (Fed. Cir. 2001); *In re Kaplan*, 789 F.2d 1574, 1579 (Fed. Cir. 1986).

Analysis

Office records indicate that the claims in Application 10/663,258 were amended, and claims 26-30 and 50-51 were cancelled, on Sept. 23, 2008, after the briefing in the present appeal was completed. Office records also indicate that the amended claims were allowed and Application 10/663,258 issued as Patent No. 7,524,814 B2 on Apr. 28, 2009. Because the provisional obviousness-type double patenting rejection is based on claims that differ from those that actually issued, we vacate the provisional obviousness-type double patenting rejection.

CONCLUSIONS OF LAW

Van Bree taught oral administration without parenteral administration to treat sepsis;

Van Bree taught N-terminal LF variants having full-length activity;

the Examiner presented a rationale to support the obviousness rejection;

at the time of Appellants' invention, there would have been a reasonable expectation of success for treating sepsis with oral LF variant administration based on the prior art; and

we vacate the provisional obviousness-type double patenting rejection.

SUMMARY

We affirm the rejection of claims 1, 7, 14, 17-19, 26-32 and 38-40 under 35 U.S.C. § 103(a) as unpatentable over Van Bree; and

We vacate the rejection of claims 1, 7-10, 14-20, 26-32 and 38-40 under the judicially created doctrine of obviousness-type double patenting over claims 16-22, 26-30 and 50-51 of copending Application No. 10/663,258.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED-IN-PART, VACATED-IN-PART

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